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Patent

REMARKS

With this response independent claim 73 and dependent claims 74-78 and 82-93 are under consideration. Claim 73 has been amended.

Interview Summary

Applicant wishes to thank the Examiner for the telephonic interview conducted with Applicant's representative on February 5, 2004. During the interview, the outstanding rejection of claim 73 as indefinite under 35 U.S.C. 112 was discussed. Specifically the term "mutagenizing at least one member of the library" was discussed. The Examiner took the position that this language implied a possible selection step which made the claim indefinite. Applicant's position was that the language merely stated what was involved in mutagenesis of a library. The Examiner agreed that the process of mutagenizing a library required that at least one member of the library undergo a mutation, but maintained the position that the "at least one" language made the term indefinite. Alternative language in which the claim simply read "subjecting the library to mutagenesis" was discussed. Applicant's representative asked the Examiner if this language would be interpreted by the Examiner to mean that any number from one, up to and including all of the members of the library had undergone mutation. Examiner agreed that this would be the proper interpretation. Based on this understanding, Applicant agreed to amend the claim. A similar discussion was held involving the term "expressing the DNA molecules of the library." It was agreed that the proper interpretation of this claim is that "expressing the DNA molecules of the library" includes situations in which any number, from one, up to and including all, members of the library are actually expressed.

Objections Under 37 C.F.R. 1.75

In the Office action, the Patent Office advised Applicant that should claim 92 be found allowable, claim 93 would be objected to under 37 C.F.R. 1.75 as being substantially duplicative. Applicant respectfully traverses this objection. Claim 92 is drawn to a method comprising screening for a reaction product, while claim 93 is drawn to a method comprising screening for enzymatic activity. Applicant respectfully submits that claims 92 and 93 differ in scope and so

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rejection under 37 C.F.R. 1.75 is improper (MPEP 706.03(k)). Not all reaction products need be the result of enzymatic activity. For example, and without limitation, a receptor-ligand complex or a protein-nucleic acid complex can be a reaction product within the scope of claim 92, but not claim 93 because their formation does not necessarily involve enzymatic activity. Due to the difference in scope between claims 92 and 93, Applicant respectfully submits that the two claims are not substantially duplicative and should be allowed.

Non Art-Based Rejections

Rejections Under 35 U.S.C. §112, Second Paragraph

In the Office action, claims 73-78 and 82-93 were rejected under 25 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention. In particular, it is alleged in the Office action that claim 73 contains two confusing steps.

Based on the meaning of the terms “subjecting the library to mutagenesis” and “expressing the DNA molecules of the library” agreed on during the interview and set forth in the interview summary above, Applicant has amended claim 73. It is Applicant’s understanding that as amended, claim 73 is not considered indefinite by the Examiner and does not require selection prior to either mutation or expression. Based on the amendment of claim 73, Applicant respectfully requests reconsideration and withdrawal of all rejections under 35 U.S.C. 112.

Art-Based Rejections

Rejections Under 35 U.S.C. § 102

In the Office action, claims 73-78 and 82-93 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,824,485 to Thompson et al. A rejection under 35 U.S.C. § 102(e) requires a showing that each element of the claim is found in a single reference, practice or device. *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). The absence of a single claimed element from a cited reference precludes a finding of anticipation. *Atlas Powder Co. v. E.I. du Pont de Nemours*, 750 F.2d 1569, 1574 (Fed. Cir. 1984).

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Applicant respectfully points out that the presently claimed invention requires that the unselected DNA molecules of the library be mutated. Applicant submits that the '485 patent does not teach or suggest the mutation of the DNA sequences contained in an unselected library.

The Office action of November 18, 2002 (Paper 20), states "[t]he gene cluster is isolate [sic] from a library constructed from a biological sample and subjected to mutation to produce a chimeric gene library which is screened for mutation." It is unclear from the Office action when this mutation step is alleged occur. The specification of the '485 is silent on the introduction of mutations except for column 10, line 15 which states that genes identified and isolated are available for mutation. This is consistent with the language of the Office action which appears to indicate that the mutation takes place after isolation of the gene cluster. As such, the mutation is conducted on a selected, i.e. isolated, gene cluster in contrast to the present claims in which unselected DNA molecules are mutated.

The citation in the Office action of chimeric gene libraries to support a mutation step suggests that the Patent Office is taking the position that the insertion of multiple inserts into a single vector constitutes mutation. Applicant submits that this is beyond the normal meaning of mutation; but even assuming for the sake of argument that such a meaning is correct, the '485 patent still does not disclose the present invention. The present claims require that the DNA molecules be mutated. Nothing in the '485 patent suggests any changes to the actual inserts. To the contrary, the '485 teaches that host cells that are permissive for recombination and lack effective DNA repair mechanisms are to be avoided (col. 17, lines 38-40 and col. 18, lines 38-39), and that host cells that are restriction-minus, endonuclease deficient, and recombination deficient are preferred (col. 42, line 66 to col. 43, line 1). Thus, in contrast to the '485 application which teaches procedures to avoid alteration of the inserted DNA, the present claims specifically require mutation of the DNA molecules of the library. Further, if the presumed meaning of mutation contained in the Office action is accepted, construction of any library would result in mutation since the mere act of inserting a DNA sequence into a vector would place the insert in association with nucleotide sequence different from that found in its natural environment.

Applicant respectfully submits that the '485 patent does not teach or suggest mutating unselected members of a library. As such, the '485 patent cannot serve as a bar to patentability

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under 37 U.S.C. § 102(e). Applicant, therefore, respectfully requests reconsideration and withdrawal of the rejection of claims 73-78 and 82-93 under 35 U.S.C. 102(e).

Rejections Under 35 U.S.C. § 103

In the Office action, claims 73-78 and 82-93 were rejected under 35 U.S.C. § 103 as being unpatentable over Thompson et al. (the '485 patent) in combination with Stemmer et al. (Proc. Natl. Acad. Sci USA 1994, 91, 10747) and Arnold et al. Applicant assumes that Arnold et al. refers to U.S. Patent No. 5,316,935 cited in Paper No. 7. Applicant respectfully renews his argument that the Patent Office has not met its burden of presenting a *prima facie* case of obviousness. Although these arguments were put forth in Applicant's response filed May 23, 2003, Applicant respectfully submits that these arguments are not addressed in the present Office action and so will be repeated here. The burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the various references and stated

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that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. SmithKline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that “[b]road conclusory statements regarding the teaching of multiple references standing alone are not ‘evidence’.” *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. “Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority.” *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

On page 6 of paper 20 the Patent Office cites *In re McLaughlin*, 443 F.2d 1392 (C.C.P.A. 1971) for the proposition that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. Applicant respectfully submits that the Office’s reliance on *McLaughlin* is misplaced. *McLaughlin* holds that hindsight is permissible in determining the knowledge of one skilled in the art at the time the invention was made. *McLaughlin* does not teach that hindsight can be used in order to select references for combination. To the contrary, *McLaughlin* cites specific language in the cited art to provide the motivation to combine. Thus, the holding in *McLaughlin* is consistent with a long line of C.C.P.A. and Federal Circuit cases holding that the use of hindsight in selecting and combining references is improper.

In addition, the Office action presents no evidence that the cited references would provide one skilled in the art with a reasonable expectation of success. Instead, the Office action states that the references would motivate one to develop various methods. For example, page 6 of paper 20 states that based on the teachings of Stemmer et al., one would be motivated to develop a method of identifying a protein with modified activity. Thus it appears that the Patent Office is attempting to construct an obvious to try argument in support of the present § 103 rejection. A determination of obviousness, however, cannot be supported by what a person skilled in the art might try or find obvious to try. Rather, the proper test requires a determination of what the prior

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art would have led the skilled person to do. *In re Tomlinson*, 363 F.2d 928 (C.C.P.A. 1966); *In re Dow Chemical*, 837 F.2d 469 (Fed. Cir. 1988).

Moreover, even when combined, the cited references do not teach or suggest the claimed invention. All of the present claims require that the members of an unselected library be subjected to a mutation process. As discussed previously, Thompson et al. teach procedures to avoid alteration of the inserted DNA. A claimed method that involves doing what a prior art reference teaches to avoid is the very antithesis of obviousness. *In re Buehler*, 515 F.2d 1134 (C.C.P.A. 1975). The deficiency found in Thompson et al. is not cured by combination with Arnold et al., Stemmer et al., or both Arnold et al. and Stemmer et al. Arnold et al. teach the production of mutated sequences encoding a single enzyme, subtilisin E. Since the starting material consists of genes encoding a single enzyme, Applicant respectfully submits that this represents mutation of a highly selected population of nucleic acids rather than the unselected nucleic acids of the present claims. Applicant also respectfully disagrees with the Office's characterization of Arnold as producing a diversified mutant library, since a library containing sequences encoding a single enzyme shows little diversity. What Arnold et al. do not teach or suggest is the mutation of members of an unselected library.

A similar situation is seen in Stemmer et al. Stemmer et al. teach the creation of shuffled genes using a human IL-1 β gene and a murine IL-1 β gene. As with Arnold et al., Stemmer et al. teach the use of highly selected populations of starting materials. In addition, Stemmer et al. teach that areas of homology averaging at least 4 bases as the minimum requirement for crossover (page 10750, col. 1), again requiring selection of the starting materials. The Office action points to nothing in Stemmer et al. that teach or suggest the mutation of unselected libraries of nucleic acids as required in the present claims.

In order to support a rejection under § 103 the combined references must teach or suggest the claimed invention. As discussed above, none of the cited references, either alone or in combination, teach or suggest the mutation of members of an unselected library. To the contrary, both Arnold et al. and Stemmer et al. use highly selected nucleic acids, and Thompson et al. specifically teach against the use of procedures that could result in mutation prior to selection. In light of the arguments stated above, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 73-78 and 82-93 under 35 U.S.C. § 103.